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(71) Applicant : **CIBA-GEIGY AG**
Klybeckstrasse 141
CH-4002 Basel (CH)

(72) Inventor : **Savastano, Louis**
21 Berkeley Place
Livingston, NJ 07039 (US)
Inventor : **Carr, James**
108 Valley Road
Butler, NJ 07405 (US)
Inventor : **Quadros, Elizabeth**
1043 Cropsey Avenue
Brooklyn, NY 11228 (US)
Inventor : **Shah, Shailesh**
416 Huntington Road
Union, NJ 07204 (US)
Inventor : **Khanna, Satish Chandra**
Spitzackerstrasse 6
CH-4103 Bottmingen (CH)

(54) Controlled release drug delivery device.

(57) An oral drug delivery device for delivering a drug either intermittently or to a pre-selected region of the gastro-intestinal tract, particularly to the colon, consists of an a solid core comprising an active agent coated with a delay jacket, then coated with a semi-permeable membrane which is optionally drilled to provide a release orifice, and then optionally further coated with an enteric material. The device delivers substantially all of the active agent to the targeted site.

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and steady drug levels in the blood, they are generally no more effective than conventional tablets in delivering the active agent primarily to the colon.

Several delivery forms have been developed which attempt to deliver active agent primarily to the colon. These methods rely upon either the environmental conditions surrounding the system, particularly pH, bacterial count and/or time.

Wong, et al. (US Patent Nos. 4,627,851; 4,693,895; and 4,705,515) disclose a tri-laminated core in which the first layer is composed of an insoluble, but semi-permeable composition, the second is a microporous combination of water insoluble polymer and osmotic solute, and the third contains an enteric composition. This dosage form has a delayed onset of delivery for a period of about two hours after it exits the stomach, after which only about 50% of the drug is released within twenty-four hours. This drug delivery time scheme is insufficient to insure that the bulk of the drug is delivered to the colon.

Theeuwes et al. (U.S. Patent No. 4,904,474) disclose a dosage form which has a two-layered internal compartment with a first layer of the drug in an excipient layer adjacent to an exit passageway and a second layer of a push component. The internal compartment is surrounded by a semi-permeable wall and then an enteric layer. This dosage form results in a delay of the onset of delivery in intestinal fluid for a period of about two hours. This represents a delay period too short, and a delivery rate too slow to insure the bulk of the drug is delivered to the colon.

Ring, et al. (WO 91/07949) disclose a tablet core coated with two laminates. The outer laminate is an erodible acrylic polymer and the inner laminate consists primarily of amylose in the glassy state which can only be degraded in the presence of fecal microflorae.

The instant parametric drug delivery devices can also be used to deliver a drug intermittently at pre-selected times such that the patient receives the drug when needed. This is of particular importance in treating diseases which have symptoms which do not remain constant throughout the day and night.

Blood pressure is known to follow a circadian rhythm during a 24-hour period. In some subjects the highest pressure occurs in the morning shortly after the individual awakes, suggesting that it would be appropriate to deliver an antihypertensive agent such as a β-blocker to such a patient sufficiently before awakening so as to mitigate the effects of the disease at the most appropriate time interval. In order to accomplish this without disturbing the patient's sleep, it is necessary to administer the drug in the evening in a form that is activated just before the patient arises.

It is accordingly an object of the present invention to provide a delivery device for the oral administration of a pharmaceutically acceptable active agent to a warm-blooded animal, either intermittently at pre-selected times or to a pre-selected region of the gastro-intestinal tract, particularly to the lower portion of the small intestine and/or the colon, more particularly to the colon.

It is another object of this invention to provide a dosage form for delivering substantially all of a therapeutic drug to the colon.

It is yet another object of this invention to provide a dosage form which comprises a core tablet coated with a delay jacket for delaying the delivery of the drug to insure the time required for the dosage form to travel through the small intestine.

It is still yet another object of this invention to provide a dosage form in which the semi-permeable membrane is still strong enough to resist the hydrostatic pressures of the osmotic core.

It is a further object of this invention to provide a dosage form which comprises an enteric coating over a semi-permeable wall for further delaying the delivery of the active agent during the time required for the dosage form to travel through the stomach.

It is still a further object of this invention to provide a dosage form which resists dissolution in gastric fluid for at least two hours, further delays initiation of active agent release for at least three hours, and releases at least 70% of its active agent within twenty-four hours.

It is yet still a further object of this invention to provide a delivery device which delivers drug intermittently at pre-selected times.

These, and other objects are accomplished by the present invention which pertains to an osmotic delivery device for the oral administration of a pharmaceutically acceptable active agent either intermittently at pre-selected times or to a pre-selected region of the gastro-intestinal tract, particularly to the lower portion of the small intestine and/or the colon, more particularly to the colon. This drug delivery device comprises:

a) a solid core comprising an active agent;

b) a delay jacket coated over the core;

c) a semi-permeable membrane coated over the delay jacket, the membrane optionally having a release orifice; and optionally

d) an enteric coating over the semi-permeable membrane.

Such device resists dissolution in gastric fluid for at least two hours and thereafter limits the release of

of organic acids such as sodium alginate, sodium ascorbate, sodium benzoate, sodium citrate, edetate disodium, sodium fumarate, sodium or potassium acetate, or magnesium succinate; organic acids such as alginic acid, ascorbic acid, citric acid, edetic acid, malic acid, or sorbic acid; carbohydrates such as dextrates, sorbitol, xylitol, maltitol, mannitol, arabinose, ribose, xylose, glucose, dextrose, fructose, galactose, mannose, sucrose, maltose, lactose, or raffinose; water-soluble amino acids such as glycine, leucine, alanine or methionine; or miscellaneous others such as magnesium sulfate, magnesium carbonate, urea, saccharin, sodium saccharin, glycerin, hexylene glycol, polyethylene glycol, or propylene glycol; and mixtures thereof.

Additional core excipients include tabletting lubricants, glidants, wetting agents to aid in dissolution of the components, binders, and suspending/thickening agents. Suitable lubricants include calcium stearate, glyceryl behenate, hydrogenated vegetable oils, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and zinc stearate. Suitable glidants include fused or colloidal silicon dioxide, calcium silicate, magnesium silicate, talc, and silica hydrogel. Suitable wetting agents include, but are not limited to, benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docusate sodium, lecithin, nonoxynol 9 or 10, octoxynol 9, poloxamer, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 50 stearate, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, 40, 60, or 80, sodium lauryl sulfate, sorbitan esters, polyoxyethylene sorbitan fatty acid esters, and Tyloxapol (4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and oxirane). Suitable binders include, but are not limited to, acacia, alginic acid, carboxymethyl cellulose sodium, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyethylene oxide, polyvinylmethacrylates, polyvinylpyrrolidone, pregelatinized starch, sodium alginate, syrup, and zein. Suitable suspending/thickening agents include acacia, agar, alginic acid, bentonite, carbomer, carboxymethyl cellulose calcium, carageenan, carboxymethyl cellulose sodium, corn starch, dextrin, gelatin, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, lecithin, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, pectin, poloxamer, polyethylene glycol alginate, polyethylene oxide, polyvinyl alcohol, polyvinylpyrrolidone, vinyl acetate, powdered cellulose, pregelatinized starch, propylene glycol alginate, silicon dioxide, sodium alginate, tragacanth, and xanthan gum.

The delay jacket is included to impede the dissolution and release of the active agent for the time necessary for the drug delivery device to travel through the small intestine. The delay jacket is capable of attracting water across the semi-permeable membrane while also hindering the water from reaching the active core for the designated period of delay. The delay jacket-will typically contain both water soluble, osmotically active components and insoluble and/or swellable components. The soluble osmotic agents leach out of the jacket and a suspension of at least some of the insoluble and/or swellable components remains. The active agent will later diffuse through this remaining suspension and thus the release of the active agent is dependent not only upon the composition of the inner core, but also upon the composition of the jacket.

The delay jacket comprises a binder, an osmotic agent, and a tablet lubricant. Suitable binders include, but are not limited to, acacia, alginic acid, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyethylene oxide, polyvinylmethacrylates, polyvinylpyrrolidone, pregelatinized starch, sodium alginate, syrup, and zein. Suitable osmotic agents include, but are not limited to, inorganic salts such as sodium, potassium or magnesium chloride, or sodium or potassium hydrogen or dihydrogen phosphate; salts of organic acids such as sodium alginate, sodium ascorbate, sodium benzoate, sodium citrate, edetate disodium, sodium fumarate, sodium or potassium acetate, or magnesium succinate; organic acids such as alginic acid, ascorbic acid, citric acid, edetic acid, malic acid, or sorbic acid; carbohydrates such as dextrates, sorbitol, xylitol, maltitol, mannitol, arabinose, ribose, xylose, glucose, dextrose, fructose, galactose, mannose, sucrose, maltose, lactose, or raffinose; water-soluble amino acids such as glycine, leucine, alanine or methionine; or miscellaneous others such as magnesium sulfate, magnesium carbonate, urea, saccharin, sodium saccharin, glycerin, hexylene glycol, polyethylene glycol, or propylene glycol; and mixtures thereof. Suitable tablet lubricants include calcium stearate, glyceryl behenate, hydrogenated vegetable oils, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

Additional jacket excipients may include glidants and wetting agents. Suitable glidants include, but are not limited to, fused or colloidal silicon dioxide, calcium silicate, magnesium silicate, talc, and silica hydrogel. Suitable wetting agents include benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docusate sodium, lecithin, nonoxynol 9 or 10, octoxynol 9, poloxamer, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 50 stearate, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20 or 40, polysorbate 60 or 80, sodium lauryl sulfate, sorbitan esters, polyoxyethylene sorbitan fatty acid esters, and Tyloxapol® (4-(1,1,3,3-tetramethylbutyl)phenol) polymer with formaldehyde and oxir-

in fluids with a pH greater than that of the stomach. Enteric coating materials include, but are not limited to, cellulose acetate phthalate NF, hydroxypropyl methylcellulose phthalate NF, polyvinyl acetate phthalate NF, and methacrylic acid copolymer NF. Thus, in a low pH environment, the enteric coating will be insoluble and hinder intrusion of water through the semi-permeable membrane which could otherwise dissolve the delay jacket. It may be applied over the semi-permeable membrane using conventional film coating techniques known in the art, for example perforated pan coating.

Upon ingestion, the drug delivery device encounters the acidic gastric fluid, but remains intact because of the enteric coating. After the stomach pushes the device through the pylorus into the duodenum, the device is exposed to fluids of higher pH and the enteric coating dissolves. Once the semi-permeable membrane is exposed to these fluids, the device is activated. Water from the gastro-intestinal tract is imbibed through the membrane by diffusion and begins to selectively dissolve the delay jacket. As the soluble components of this delay jacket are selectively dissolved, they are released either through the membrane, or through the release orifice, until they are depleted. The delay jacket directly under the membrane prevents water from reaching the active drug core, thus providing the delayed release of the active agent. Once the delay jacket has been exhausted of soluble components, a suspension of insoluble material held in place by the membrane, continues to surround the active drug core. Eventually, the active core is reached by the water, increasing the pressure within the membrane as the core osmotic agents imbibe more and more water. As the drug is dissolved or suspended, this hydrostatic pressure forces the active agent through the membrane and/or through the release orifice to deliver the drug at a controlled rate. The release rate of the drug is based on the osmotic properties of the core, the solubility of the drug and excipients, and the water permeation rate through the membrane, and to a more limited extent, the viscosity of the solution or suspension, the suspension of material from the depleted delay jacket, and the size of the membrane pores or release orifice.

As an extension to the basic device, a further layer of active agent may be included to deliver an initial burst of active agent prior to the device reaching the colon. This active agent may be the same as or different from that within the core. The additional active agent layer may be applied over the enteric coating to deliver an immediate release of active agent. Alternatively, this additional layer may be applied under the enteric layer for release in the upper portion of the small intestine.

To deliver active agent intermittently, the basic device is altered by including an additional layer of active agent between the delay jacket and the membrane. This active agent layer comprises an active agent and may optionally include other pharmaceutically acceptable excipients including osmotic agents, lubricants, glidants, wetting agents, binders, fillers, and suspending/thickening agents.

The following examples are presented to further illustrate and explain the present invention and should not be taken as limiting in any regard.

Example 1 - Preparation of colonic delivery device

A colonic delivery device is prepared from the following ingredients:

following parameters:

Inlet Air Temperature	50-65°C
Atomizing Air Pressure	2.5 Bar
Nozzle Size and Type	1.1 mm, 35°
Spray Rate	15.22 ml/min

Example 2 - Dissolution test

The release rate of a tablet of Example 1 is determined using a two-hour presoak in 0.1N HCl and then a standard dissolution test using USP Rotating Basket and the following parameters:

Stir Rate	100 rpm
Wavelength	275 nm
Temperature	37°C
Medium	0.1 N HCL: 0-2 hr; phosphate buffer (pH=7.5): 2.24 hr

The results of the dissolution test are as follows:

Timepoint (hours)	Total Release (%Total)	Rate (%/hr)
0-2	<0.5	negligible
3-5	<0.5	negligible
6	1.7	1.3
7-8	16.5	7.4
9-10	33.6	8.6
11-12	48.3	7.4
13-14	61.0	6.4
15-18	76.2	3.8
19-24	82.7	1.1

Example 3 - Aqueously administrable semi-permeable membrane

A controlled release delivery device in which the semi-permeable membrane is applied aqueously is prepared from the following ingredients:

Example 4 - Preparation of an Intermittent Device

Ingredient	Quantity
Placebo Core	per tablet (mg)
dextrates	178.0
hydroxypropyl methylcellulose, 15 cps	10.0
polyethylene glycol 8000	10.0
magnesium stearate	2.0
Drug Sub-coat	per 1000g of solution (g)
phenylpropanolamine HCl	126.0
hydroxypropyl methylcellulose, 15 cps	25.0
polyethylene glycol 8000	10.0
deionized water	839.0
Delay Jacket	per tablet (mg)
dextrates	409.0
hydroxypropyl methylcellulose, 15 cps	23.2
polyethylene glycol 8000	23.2
magnesium stearate	4.6
Semipermeable Membrane	per 1000g of dispersion (g)
cellulose acetate 398-10 (25% aqueous dispersion)	121.2
glyceryl triacetate	45.5
hydroxypropyl methylcellulose, 15 cps	3.3
talc	3.3
deionized water	826.7
Drug Over-coat	per 1000g of solution (g)
phenylpropanolamine HCl	98.0
hydroxypropyl methylcellulose, 15 cps	11.0
polyethylene glycol 8000	22.0
deionized water	869.0

All core components are mixed together and sized. The mixture is then pressed into tablet cores using conventional tabletting techniques.

To prepare the sub-coat, heat approximately one-third of the water to near boiling and add the hydroxypropyl methylcellulose followed by the polyethylene glycol with stirring. Remove from heat and add the Phe-

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EUROPEAN SEARCH REPORT

Application Number
EP 94 81 0212

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X	EP-A-0 425 699 (CHUGAI SEIYAKU KABUSHIKI KAISHA) * claim 1 * * page 3, line 1 - line 51 * * page 4, line 30 - line 39 * * page 6; example 8 * -----	1-6	A61K9/28 A61K9/00
			TECHNICAL FIELDS SEARCHED (Int.Cl.5) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	4 August 1994	Ventura Amat, A

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